Please add new claims 19 and 20 as follows:

--19. (new) A method of treating pathologies characterized by a deleterious accumulation of extracellular matrix in a tissue, comprising contacting the tissue with an agent that inhibits the functional interaction of TGF-ß with its cell-surface receptor in the tissue thereby inhibiting the accumulation of a TGF-ß induced component of the extracellular matrix in the tissue.--

--20. (new) A method of inhibiting the accumulation of a TGF-ß induced component of extracellular matrix in a tissue, comprising contacting the tissue with an effective amount of an agent that inhibits the functional interaction of TGF-ß with its cell-surface receptor in the tissue.--

REMARKS

Applicants wish to thank the Examiner for granting a personal interview with their representative, Antoinette F. Konski, and Dr. Michael Pierschbacher on April 23, 1993. The interview was helpful in clarifying the rejections of the claims and removing the rejection of claims 2 and 7 under 35 U.S.C. § 112, second paragraph.

Claims 1, 2, 5-7, 10 and 13-15 are pending and were rejected by the Examiner in the outstanding Office Action. Claims 1, 2, 5, 6, 7, 10 and 13 have been amended and new claims 19 and 20 have been added. Support for the term "a component of the extracellular matrix" introduced into claims 1 and 6 is found in the specification on page 2, lines 9 and 19, page 7, lines 28 to 29 and page 8, lines 1 to 2. Support for amended claim 1 is found in the specification on page 25, lines 16 to 19. Amended claim 13 is

supported in the specification on page 7, lines 15 to 18, page 9, lines 5 to 6 and page 9, line 28 to page 10, line 4. New claims 19 and 20 are supported in the specification on page 2, lines 9 and 19, page 7, lines 28 to 29 and page 8, lines 1 to 2, page 10, line 1, page 13, lines 18 to 27, page 21, lines 28 to 30 and page 25, lines 16 to 19. Claims 2 and 5 have been amended to also depend on newly added claim 19 and claims 7 and 10 have been amended to also depend on newly added claim 20. Thus, the amendments to the claims and the addition of new claims 19 and 20 do not raise an issue of new matter. Entry thereof is respectfully requested.

In view of the preceding amendments and the remarks which follow, Applicants respectfully request that the Examiner reconsider and withdraw the outstanding rejections of the claims.

I. OBVIOUSNESS-TYPE DOUBLE PATENTING

The claims stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-4, 8, 27 and 30 of copending application serial no. 07/467,888 and over claims 1-8 and 12-24 of copending application Serial No. 07/803,285. Applicants reserve their right to respond to these rejections when allowed subject matter has been indicated in any of the allegedly conflicting applications.

II. REJECTIONS UNDER 35 U.S.C. §112, FIRST AND SECOND PARAGRAPHS

Claims 1, 2, 5-7 and 10 stand rejected under 35 U.S.C. §

112, first and second paragraphs.[1] The Examiner alleges that the term "TGF-ß specific inhibitory agents" is descriptive only of anti-TGF-ß antibodies because there is no indication Applicants' peptides or protein interacts with TGF-ß. According to the Examiner, the peptide or protein is known in the art to interact with the TGF-ß binding site, which is not the same as interacting with TGF-ß itself.

The Examiner also alleges that the phrase "extracellular matrix" is not supported by the specification. The Examiner reasons that Applicants have only shown effectiveness against two components of the extracellular matrix, namely, biglycan and decorin.

Applicants traverse the Examiner's rejections for these reasons.

Independent claims 1 and 6 have been amended to recite in pertinent part contacting the tissue with a "TGF-ß inhibitory agent which suppresses the accumulation of a TGF-ß induced component of the extracellular matrix...." Thus, the inhibitory agent is defined by its ability to suppress the accumulation of a component of the extracellular matrix in the tissue. The agent is not defined by its ability to bind TGF-ß or to its receptor site, as the Examiner appears to reason.

In addition, without conceding to be bound by any one theory concerning how one of skill in the art can prohibit the

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[1] The rejection of claims 2 and 7 under 35 U.S.C. § 112, second paragraph was removed by the Examiner during the April 23, 1993 interview.

extracellular matrix stimulatory activity of TGF-ß[2] in a tissue, and merely to advance prosecution of this application, Applicants have added new claims 19 and 20 which define the "agent" by the function of inhibiting the functional interaction of TGF-ß with its receptor on the surface of a cell in the tissue. This language was selected during the April 23, 1993 interview with the Examiner. However, Applicants retain the right to pursue claims of different scope in this application or a later filed application.

Additionally, Applicants' claims now more specifically recite that the agent affects at least one component of the extracellular matrix in the tissue. Nevertheless, the net effect remains a reduction in the deleterious accumulation of extracellular matrix as well as an effective method for treating pathologies characterized by a deleterious accumulation of extracellular matrix.

Claim 5 remains rejected for Applicants' alleged failure to present evidence that the claimed method is effective against pathologies other than glomerulonephritis. The Examiner states that Applicants' implicit assertion that all deleterious extracellular matrix accumulations are related to TGF-ß is speculative and lacking evidence to the contrary.

In response to the Examiner's rejection, Applicants direct the Examiner's attention to the following publications:

1. Gressner, A.M., Liver fibrosis: perspectives in pathobiochemical research and clinical outlook,

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[2] All agents having such function are within Applicants' intended scope of claims 1 and 6.

Eur. J. Clin. Chem. Clin. Biochem. Vol. 29(5):293-311 (May, 1991);

2. Fausto, N., et al., Effects of TGF-betas in the liver: cell proliferation and fibrogenesis, Ciba Found. Symp. Vol. 157:165-74 (1991);

3. Limper, A.H. and Roman, I., A versatile matrix protein with roles in thoracic development, repair and infection, Chest Vol. 101(6):1663-73 (June 1992); and

4. Lissoos, T.W. and Davis, B.H., Pathogenesis of Hepatic Fibrosis and the Role of Cytokines, J. Clin. Gastroenterol. Vol. 15(1):64-68 (1992).

Publications (1), (2) and (4) disclose the role of TGF-ß in the pathological accumulation of extracellular matrix ("ECM") in liver disease and publication (3) discloses the role of increased expression of fibronectin (an ECM glycoprotein) in the development of ARDS. A copy of each of these articles is attached for the Examiner's convenience and listed on the attached PTO Form 1449. Accordingly, in view of the attached teachings of these publications, Applicants have provided evidence beyond mere speculation regarding the relationship between deleterious extracellular matrix accumulations and TGF-ß in glomerulonephritis, liver disease and ARDS. Removal of the rejection of claim 5 is respectfully requested.

Claims 1, 2, 5-7 and 10 stand rejected under 35 U.S.C. § 112, first paragraph on the ground that the disclosure allegedly is enabling only for claims limited to an antibody. The Examiner

asserts that the specification fails to disclose evidence showing that the peptides would work in an in vivo setting. The Examiner requests that the claims be limited to anti-TGF-ß antibodies reasoning that agents other than antibodies are not specific for TGF-ß nor is it apparent how such factors could localize to the desired site to exert any influence in an in vivo setting. Applicants traverse the Examiner's rejection for the reasons which follow.

First, Applicants respectfully request that the Examiner remove the rejection of claims 2 and 7 on this ground as they are specifically limited to the agent being an anti-TGF-ß antibody. Secondly, Applicants direct the Examiner's attention to Example VIII of the application presented on pages 24 and 25 of the disclosure. Using a scientifically accepted in vitro experimental model, Applicants show that the peptide blocked the proteoglycan producing effect of exogenously added TGF-ß in cultures of rat mesangial cells. Applicants' Examples I, III, IV and VII establish that the in vitro model used by Applicants in Example VIII, is predictive of in vivo success.

Regarding the Examiner's concerns of effective in vivo localization of peptides, Applicants point out that localization systems are well known in the art and can be selected or designed for targeting to tissue. Applicants further direct the Examiner's attention to the attached article by Border, W.A. et al., Natural inhibitor of transforming growth factor-ß protects against scarring in experimental kidney disease, Nature, Vol. 360:361-64 (1992) wherein it was shown that without the use of any targeting system or carrier, intravenously administered decorin inhibited TGF-ß induced deposition of extracellular matrix in injured glomeruli from nephritic rats (see column 2, page 362). Thus, based on the

above, it appears that concerns regarding in vivo localization of peptides or proteins have been addressed.

In view of the preceding amendments and remarks, Applicants respectfully request that the rejections of the claims under 35 U.S.C § 112, first and second paragraphs be removed.

III. REJECTION UNDER 35 U.S.C. § 102

Claims 13-15 stand rejected under 35 U.S.C. § 102 over the disclosure of Bassol et al. However, in view of Applicants' amendment of the claims to TGF-ß inhibitory agents that are not general protein inhibitor agents, Applicants respectfully request that the Examiner remove the rejection of the claims as allegedly anticipated by Bassol et al.

IV. REJECTIONS UNDER 35 U.S.C. § 103

Claims 1, 2, 6 and 7 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Connor et al. The Examiner alleges that Connor et al. disclose an in vitro model system of intraocular fibrosis (a pathology characterized by extracellular matrix accumulation) by using antibodies. The Examiner states that Connor et al. also disclose that 84-100% of the TGF-ß activity could be blocked using antibodies to TGF-ß. The Examiner further alleges that Connor et al. only differs from the rejected claims in that the reference fails to disclose in vivo usage of the antibodies for treating fibrosis, a difference that is suggested on page 1665, second column, last paragraph of the reference.

Applicants traverse the Examiner's rejection. The amended claims now are directed to a method of inhibiting the

accumulation of a TGF-ß induced component of the extracellular matrix in a tissue and a method for treating pathologies characterized by a deleterious accumulation of extracellular matrix in a tissue. The methods comprise contacting the tissue with an effective amount of a TGF-ß inhibitory agent to suppress the accumulation of a component of the extracellular matrix thereby decreasing deleterious accumulation of the extracellular matrix to treat the pathology. In new claims 19 and 20, the agents are defined by their ability to inhibit the functional interaction of TGF-ß with its cell surface receptor.

Connor et al., on page 1663, col. 1, disclose that an antibody against TGF-ß blocked the **growth inhibitory** activity of TGF-ß in **cultures of CCL 64 cells and NRK cells** in soft agar. Connor et al. do not disclose that the anti-TGF-ß antibodies were able to block TGF-ß's role in the deleterious accumulation of extracellular matrix in a tissue. In the last paragraph bridging pages 1665 and 1666 of the article the authors state that: "The final determination of the role of TGF-ß in this disease process awaits the ability to block its activity and assess if this can retard or arrest fibrosis." The authors make no conclusions regarding the ability of the antibodies to block TGF-ß's ability to induce accumulation of ECM and **invite further experimentation** in column 1, page 1666: "The role of TGF-ß in fibrosis of other organs and the assessment of the relative roles of TGF-$ß_2$ and TGF-$ß_1$ in these disease processes deserve further investigation."

Claims 5 and 10 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Connor et al. as applied to claims 1, 2, 6 and 7, above, and further in view of MacKay et al. The Examiner asserts that MacKay et al. disclose the relationship between TGF-ß and the proliferation of glomerular cells and the

accumulation of mesangial matrix in progressive glomerular nephritis. The Examiner states that it would have been obvious to one of ordinary skill in the art to substitute glomerular tissue for the ocular tissue of Connor et al. to obtain Applicants' methods once the ability of the antibody to block TGF-ß activity was successfully demonstrated. The Examiner further states that it would have been obvious to apply the concept to diseases characterized by excess TGF-ß production and having increased extracellular matrix production since the ability of the antibody to bind to TGF-ß is irrespective of tissue location or cell type.

Applicants traverse the Examiner's rejection of claims. Claim 5 is directed to a method of treating glomerulonephritis, ARDS and cirrhosis of the liver by contacting the affected tissue with an agent which inhibits the functional interaction of TGF-ß with its cell-surface receptor in the tissue and thereby inhibiting the accumulation of a TGF-ß induced component of the extracellular matrix, or alternatively, by contacting the tissue with a TGF-β inhibitory agent which suppresses the accumulation of a TGF-β induced component of the ECM in the tissue. Claim 10 is directed to a method of inhibiting the accumulation of a TGF-ß induced component of the extracellular matrix in a tissue having cells selected from the group consisting of kidney, lung, liver and skin cells by contacting the tissue with an effective amount of an agent that inhibits the functional interaction of TGF-ß with its cell-surface receptor in the tissue, or alternatively, by contacting the tissue with a TGF-β inhibitory agent which suppresses the accumulation of a TGF-β induced component of the ECM in the tissue.

In MacKay et al., Applicants note that all but one reported study were done on cultured glomerular endothelial, epithelial and mesangial cells that were substantially homogenous. No organ tissue culture or <u>in vivo</u> studies were disclosed.

In column 1 on page 1183, MacKay et al. report that TGF-ß inhibited the proliferation of low density mesangial cells in culture and for high density cells in culture, it exhibited a proliferative response.[3] For all other cell types assayed, TGF-ß inhibited proliferation regardless of cell density (see page 1183, column 1). MacKay et al. also disclose that TGF-ß increased production of collagen and fibronectin synthesized by mesangial cells in culture (see page 1183, column 2). However, TGF-ß failed to increase production of collagen by glomerular epithelial cells in culture while it also increased fibronectin production by glomerular epithelial (see page 1183, column 2). MacKay et al. further disclose that TGF-ß receptors were found in cultures of all cell types tested and on intact glomeruli removed from rats. In this regard, on page 1183 in column 2, MacKay et al. report that the receptors for TGF-ß on the intact glomeruli cells were of lesser affinity than that found in cell culture.

For some kidney cell types tested, MacKay et al. do report that TGF-ß increased production of a proteoglycan that was released into the culture medium. But increased production of a proteoglycan than can be found as a component of the ECM does not mean the proteoglycan accumulates in the ECM. Thus, MacKay et al. did not show nor suggest that TGF-ß was responsible for the production of a component of the extracellular matrix in a tissue. No studies were reported regarding extracellular matrix production. Regarding lung cells, liver cells, skin cells, cirrhosis of the liver and ARDS, MacKay et al. is completely silent. Thus, MacKay et al. do not teach nor suggest the methods of claims 5 and 10.

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[3] A response which is contrary to that what one might expect for high density cells in culture.

The references also fail to disclose any motivation to combine them in the manner the Examiner has suggested. Connor et al. show that anti-TGF-ß antibodies block the growth inhibitory activity of TGF-ß in vitro; the publication also teaches that administration of TGF-ß alone did not result in increased formation of fibrosis. Connor et al. did not assay for TGF-ß's ability to induce proteoglycan production in vitro, in vivo, nor for TGF-ß's effect on deleterious accumulation of extracellular matrix in a tissue. MacKay et al. show that the activity of TGF-ß (alone) on cell growth varied with cell type and show that TGF-ß (alone) inhibited the production and secretion into the culture medium of some components of the extracellular matrix and increased the production of others. MacKay et al. did not show that the component affected the accumulation of ECM in the tissue. Thus, neither reference provides a teaching to motivate the skilled artisan to combine them.

Accordingly, in view of the preceding amendments and remarks, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 103.

V. CONCLUSION

In light of the foregoing remarks, Applicants respectfully request the Examiner withdraw all rejections of the claims and earnestly solicits an allowance of the same.

No fee, other than the enclosed fee for a two month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, the Examiner is authorized to charge this fee to Deposit Account No.

03-0370. The Examiner is invited to call Cathryn A. Campbell, Esq. or the undersigned attorney if there are any remaining issues.

Respectfully submitted,

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